(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: **0 004 187**
A1

(12) # EUROPEAN PATENT APPLICATION

(21) Application number: 79300351.8

(22) Date of filing: 07.03.79

(51) Int. Cl.²: C 07 D 401/12
C 07 D 213/82, C 07 D 417/12
C 07 D 277/56, A 61 K 31/455
A 61 K 31/41, A 61 K 31/47
//C07D413/12, C07D213/81,
C07D215/54, C07D261/18,
C07D275/02, C07D275/04,
C07D307/68, C07D407/12,
C07D263/34, C07D285/06,
C07D285/10

(30) Priority: 09.03.78 US 884858

(43) Date of publication of application:
19.09.79 Bulletin 79/19

(84) Designated contracting states:
BE CH DE FR GB IT LU NL SE

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(54) **Heterocyclylcarbonyl derivatives of urea and their use as agents for dissolution of gallstones.**

(57) Heterocyclocyclylcarbonyl derivatives of urea for use in dissolving gallstones, having the formula $RCONHCONR^1R^2$, wherein R is pyridyl, monochloro-pyridyl, quinolyl, furyl, thiazolyl, 4-methyl-5-thiazolyl, 4-methyl-5-oxazolyl, isothiazolyl, 3-methyl-5-isothiazolyl, 3-(1,2-benzoisothiazolyl), 5-methyl-3-isoxazolyl, 3-methyl-5-isoxazolyl, 5-methyl-3-phenyl-4-isoxazolyl, 3-(1,2,5-thiadiazolyl) or 4-(1,2,3-thiadiazolyl); R^1 is hydrogen, alkyl having from one to ten carbon atoms naphthyl or phenyl; R^2 is hydrogen, alkyl having from one to ten carbon atoms, phenyl or phenylalkyl wherein the alkyl has from one to four carbon atoms; or R^1 and R^2 taken together with the nitrogen to which they are attached form a morpholino, thiomorpholino, 1-(1,2,3,6-tetrahydropyridyl), 1-azacycloheptyl, 1-azacyclooctyl or 3-(2,3,4,5-tetrahydro-3,1-benzazepinyl) group, or a piperidino group optionally substituted with alkyl having from one to four carbon atoms, alkoxy having from one to four carbon atoms, chloro, or phenylalkyl having from one to four carbon atoms in the alkyl group; with the proviso that, where R is a 5-methyl-3-isoxazolyl group, then R^1 and R^2 are taken together with the nitrogen to which they are attached and form a group other than morpholino. These compounds are novel, except for those in which R is pyridyl, R^1 is hydrogen and R^2 is hydrogen, methyl or ethyl.

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Croydon Printing Company Ltd.

DESCRIPTION

"Heterocyclylcarbonyl Derivatives of Urea and their use as Agents for Dissolution of Gallstones"

This invention relates to heterocyclylcarbonyl derivatives of urea for use as agents for the dissolution of gallstones, and in particular of cholesterol gallstones. The invention also provides novel heterocyclylcarbonyl ureas.

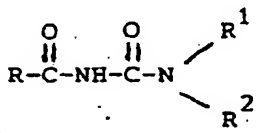
Cholelithiasis, one of the most common disease of Western civilisation, is under intensive investigation to determine not only the physio-chemical changes in bile which lead to cholesterol gallstone formation, but also how gallstones, once formed, can be dissolved. An excellent summary of the current state of such efforts is presented by Bell in Gut, 15, 913-929 (1974).

Many attempts have been made to indirectly dissolve cholesterol gallstones by dietary manipulation or by oral administration of a compound so as to alter the composition of bile secreted by the liver and thus reverse the pathogenic process of cholelithiasis. Recently, prevention and even reversal of the pathogenic cholelithiasis process in man has been reported by the administration of chenodeoxycholic acid (U.S. Patents 3,859,437 and 3,969,503, issued January 7, 1975 and July 13, 1976, respectively), a substance believed to inhibit synthesis of cholesterol in the body.

A number of different heterocyclylcarbonyl ureas have been disclosed previously: U.S. Patent 4,014,876 issued March 29, 1977, disclosed a series of 1-(3-isoxazolylcarbonyl)ureas as hypoglycemic and/or blood free-fatty acid normalising antidiabetic agents;

Samejima in Yakugaku Zasshi 80, 1706-12 (1960)(Chemical Abstracts 55, 10439h) reported preparation of several 1-(nicotinoyl)ureas as solubilising agents; Guttman and Platek in J. Pharm. Sci. 56, 1423-7 (1967) described 1,2-dihydro-1-methyl-2-oxoquinoxalinyl-3-carbonyl urea as a base-catalysed degradation product of 9-methylisoalloxazine; while several pyrazinylcarbonyl ureas useful as diuretics are described in U.S. Patent 3,345,372, issued October 3, 1967.

According to the present invention there are provided for use in dissolving gallstones heterocyclylcarbonyl ureas having the formula:



wherein R is pyridyl, monochloro-pyridyl, quinolyl, furyl, thiazolyl, 4-methyl-5-thiazolyl, 4-methyl-5-oxazolyl, isothiazolyl, 3-methyl-5-isothiazolyl, 3-(1,2-benzisothiazolyl), 5-methyl-3-isoxazolyl, 3-methyl-5-isoxazolyl, 5-methyl-3-phenyl-4-isoxazolyl, 3-(1,2,5-thiadiazolyl) or 4-(1,2,3-thiadiazolyl);

R^1 is hydrogen, alkyl having from one to ten carbon atoms naphthyl or phenyl;

R^2 is hydrogen, alkyl having from one to ten carbon atoms, phenyl, or phenylalkyl wherein the alkyl has from one to four carbon atoms;

or R^1 and R^2 taken together with the nitrogen to which they are attached form a morpholino, thiomorpholino, 1-(1,2,3,6-tetrahydropyridyl), 1-azacycloheptyl, 1-azacyclooctyl or 3-(2,3,4,5-tetrahydro-3,1-benzazepinyl) group, or a piperidino group optionally substituted with alkyl having from one to four carbon atoms, alkoxy having from one to four carbon atoms, chloro, or phenylalkyl having from one to four carbon atoms in the alkyl group;

with the proviso that, when R is a 5-methyl-3-isoxazolyl group, then R^1 and R^2 are taken together with the nitrogen to which they are attached and form a group other than morpholino;

and the pharmaceutically acceptable acid addition salts of those compounds wherein R is a basic group.

These compounds are particularly valuable agents for the dissolution of cholesterol gallstones in mammals, including humans. Additionally, they reduce biliary lipid pools in mammals.

Also provided by the invention are novel heterocycylcarbonyl ureas as defined above, with the further proviso that, when R is 3-pyridyl, and R^1 is hydrogen, R^2 is other than hydrogen, methyl or ethyl.

Pharmaceutically acceptable acid addition salts of those compounds wherein R is a basic group, e.g. pyridyl, include the hydrochloride, hydrobromide, sulfate, phosphate, pamoate, citrate, malate, fumarate, tartrate, glycolate, maleate, p-toluenesulfonate, succinate, oxalate, mandelate, acetate and lactate salts. Such salts are prepared by known procedures.

The favoured compounds of this invention are those in which R^1 is hydrogen and R^2 is a phenylalkyl group, or in which R^1 and R^2 are taken together with the nitrogen to which they are attached to form a ring structure, especially a 6-membered ring. Preferred compounds are those in which R is pyridyl, chloro-substituted pyridyl or 3-quinolyl and either R^1 is hydrogen and R^2 is benzyl, or NR^1R^2 is a 1-(1,2,3,6-tetrahydropyridyl) or optionally-substituted piperidino group.

The compounds of this invention are readily prepared by reaction of the appropriate hetercyclylcarbonyl isocyanate (R-CO-N=C=O) with desirably an excess of an appropriate amine of formula HNR^1R^2 in a reaction-inert solvent at a temperature of from about 0°C to about 100°C (Method A). The favoured temperature range is from about 20°C to about 50°C since the reaction proceeds satisfactorily within this temperature range as regards reaction rate and yield of product. Alternatively, they can be prepared by reacting the appropriate heterocyclylcarboxamides ($R-CONH_2$) with an appropriate isocyanate ($R^2-N=C=O$) under conditions similar to those described above. This latter procedure, of course, affords products having only one substituent (R^2) on the terminal nitrogen of the desired product. Representative solvents for these reactions are methylene chloride, ethylene dichloride, tetrahydrofuran, dioxane, diethyl ether, dimethyl ether of ethylene glycol, benzene, toluene and xylene.

A further procedure comprises reacting the appropriate 1-heterocyclyl-3,3-diphenylurea with an appropriate amine (HNR^1R^2) in a reaction inert solvent at an elevated temperature in the presence of an acid (Method B).

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Temperatures of from about 50°C to about 200°C are suitable for the reaction. The favoured range is from about 85°C to about 150°C. Suitable solvents for this procedure are those enumerated above, the boiling points of which fall within the temperature range cited.

The presence of an acid expedites the reaction. The acid can be added separately to the reaction mixture or can be added as an acid addition salt of the amine reactant. The acid and amine are generally used in equimolar ratios. The ratio of acid to amine, however, is not critical but can vary from trace amounts of acid to up to several molar excesses. The favoured ratio of acid to amine is from about 2:1 to about 1:2.

A still further procedure comprises acylation of a urea derivative of the formula $H_2N-CO-NR^1R^2$ with an appropriate heterocyclyl acid chloride R-COCl in a reaction inert solvent, that is, a solvent which does not react to any appreciable extent with the reactants or products. Suitable solvents includes alkanols having from one to four carbon atoms, halogenated hydrocarbons such as methylene chloride, chloroform, carbon tetrachloride, and hydrocarbons such as benzene, toluene, xylene, n-hexane, and cyclohexane. An acid acceptor is also used. Representative acid acceptors for use in the above solvent systems are tertiary organic bases such as triethylamine, pyridine, collidine picoline and alkali metal alkoxides. Water can also be used as solvent since reaction occurs primarily and preferentially with the urea reactant.

When using water as solvent, typical Schotten-Baumann reaction conditions are employed. Regardless of the solvent system used, the reaction is usually conducted at a temperature of from about 10°C to about 100°C.

Another suitable procedure comprises reacting a lower alkyl ester of a heterocyclic carboxylic acid R-COOR^3 wherein R is as previously defined and R^3 is lower alkyl having up to four carbon atoms with the sodium (or potassium) salts of an appropriate urea reactant of the formula NaHN-CO-NR^{1}R^2 in a reaction inert solvent such as chloroform, N,N-dimethylformamide, toluene and tetrahydrofuran at a temperature of from about -10°C to about 70°C.

The requisite isocyanates of formula R-CO-N=C=O are conveniently prepared by reaction of the corresponding amide with oxalyl chloride in a reaction inert medium such as ethylene dichloride, xylene, toluene at temperatures from about 0°C to about 100°C. A slight excess, up to 10%, of oxalyl chloride is generally used to insure complete reaction of the amide. The isocyanate need not be isolated from the reaction mixture. In actual practice, it has been found most convenient to add the amine reactant HNR^{1}R^2 directly to the isocyanate containing reaction mixture.

When the isocyanate reactants are of the formula R^2-N=C-O they are prepared by reaction of the appropriate primary amine R^{2}NH$_2$ with phosgene under reaction conditions similar to those described above.

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The amide reactants used to prepare the isocyanate reactants described above are in turn prepared from the corresponding nitriles by hydrolysis according to known procedures. A convenient procedure comprises reaction of the nitrile with an alkali metal hydroxide, e.g. potassium hydroxide, and hydrogen-peroxide in a solvent such as ethanol at temperatures from about room temperature to the reflux temperature until evolution of gas is complete. Alternatively, they are prepared by amidation of the corresponding acid chlorides according to well known procedures. The acid chlorides are prepared by reaction of the appropriate carboxylic acid with thionyl chloride, the latter generally serving as reactant and solvent.

The compounds described herein are useful in dissolving gallstones in mammals and, when used for such purpose, are administered orally or parenterally in unit dosage form either alone or in the form of pharmaceutical preparations; that is, in combination with other therapeutic agents and/or a pharmaceutically acceptable carrier, the latter selected on the basis of the chosen route of administration and standard pharmaceutical practice. For example, they can be combined with various pharmaceutically acceptable inert carriers in the form of tablets, capsules, lozenges, troches, hard candies, powders, aerosol sprays, aqueous suspensions or solutions, injectable solutions, elixirs, syrups and the like. Such carriers include solid diluents or fillers, sterile aqueous media and various non-toxic organic solvents.

Moreover, the oral pharmaceutical compositions of this invention can be suitably sweetened and flavoured by means of various agents of the type commonly used for this purpose.

The particular carrier selected and the proportion of active ingredient to carrier are influenced by the solubility and chemical nature of the therapeutic compounds, the chosen route of administration and the needs of standard pharmaceutical practice. For example, when the compounds of this invention are administered orally in tablet form, excipients such as lactose, sodium citrate, calcium carbonate and dicalcium phosphate can be used. Various disintegrants such as starch, alginic acids and certain complex silicates, together with lubricating agents such as magnesium stearate, sodium lauryl sulphate and talc, can also be used in producing tablets for the oral administration of these compounds. For oral administration in capsule form, lactose and high molecular weight polyethylene glycols are among the preferred materials for use as pharmaceutically-acceptable carriers. Where aqueous suspensions are to be used for oral administration, the compounds of this invention can be combined with emulsifying or suspending agents. Diluents such as ethanol, propylene glycol, glycerine and chloroform and their combinations can be employed as well as other materials.

For the purpose of parenteral administration, solutions or suspensions of these compounds in sesame or peanut oil or in aqueous propylene glycol solutions can be employed, as well as sterile aqueous solutions of the soluble pharmaceutically-acceptable salts described herein.

These particular solutions are especially suited for intramuscular and subcutaneous injection purposes should such method of administration be desired. The aqueous solutions, including those of the salts dissolved in pure distilled water, are also useful for intravenous injection purposes provided that their pH is properly adjusted beforehand. Such solutions should also be suitably buffered, if necessary, and the liquid diluent first rendered isotonic with sufficient saline or glucose.

It is necessary that the active ingredient form a proportion of the composition such that a suitable dosage form will be obtained. Obviously, several dosage unit forms can be administered at about the same time. Although compositions with less than 0.005% by weight of active ingredient might be used in certain instances, it is preferred to use compositions containing not less than 0.005% of the active ingredient; otherwise, the amount of carrier becomes excessively large. Activity increases with the concentration of the active ingredient. The composition may contain 10, 50, 75, 95 or an even higher percentage by weight of the active ingredient.

The dosage unit administered can be any gallstone dissolving effective amount. Dosages of from about 10 mg/kg to about 100 mg/kg per day, and preferably from about 10 mg/kg to about 50 mg/kg per day are effective in achieving the desired effect.

In addition to the above mentioned methods of administration, the compounds of this invention can be administered by intraductal infusion, a method of considerable value in the treatment of patients having stones retained in the common bile duct after cholecystectomy and common duct exploration. It is of particular value in situations where the gallstones are between the T-tube and the duodenum. A convenient dosage form for this method is a saline solution buffered to pH 7.5. Concentrations of from about 10 millimoles to about 200 millimoles of the chosen compound are practical for such use. The solutions are allowed to drip into the duct at a rate of 30 ml per hour for periods of from 3 to 14 days.

The value of the herein-described compounds as agents for the dissolution of gallstones arises from their ability to decrease the lithogenic index; i.e. the relative concentrations of the three major bile lipids: cholesterol, bile acids and phospholipids. It expresses the cholesterol level as a percentage of the concentration that would be required to saturate bile of that particular bile acid and phospholipid concentration or, it is 100 times the ratio of cholesterol actually present to the maximal amount that would be soluble at the phospholipid-bile acid ratio of a given sample.

The effects of the compounds described herein, and their efficacy are dependent upon their increase in bile acid synthesis in vivo. The compounds increase the conversion of cholesterol to bile acids by increasing the activity of the rate-controlling enzyme, cholesterol 7α-hydroxylase.

The direct measurement of bile acid synthesis in vivo and, hence, the determination of the ability of these compounds to dissolve gallstones is accomplished according to the procedure of Sjovall, Meth. Biochem. Anal., 12, 123 (1964). In this procedure, male albino mice, weight ca. 25 gm., are adapted to a synthetic diet (sucrose, casein, corn oil, salts and vitamins) for 1-2 weeks. They are then fed the test compounds mixed into their diet (maximum 0.15%) for 4 days. One day before sacrifice (3 days on drug), the mice are injected i.p. with 0.2 ml of solution containing (in 35 ml) 10 µc 3H-cholic acid, 50 µc ^{14}C-cholesterol (both carrier free), 2% bovine serum albumin, and 0.9% NaCl. Food consumption and initial and final body weights are recorded for each group. The animals are sacrificed 24 hours after injection by decapitation and exsanguination. The small intestine of each animal is removed, and its contents rinsed into a screw-cap 30 ml polypropylene tube with 10 ml saline. Saturated KOH (2.5 ml) and carrier taurodeoxycholate are added to each tube, and the tubes autoclaved at 15 p.s.i. for 4 hours. The contents are acidified with 4 ml concentrated HCl and extracted with 2 x 15 ml ethyl acetate. The extracts are combined, dried over anhydrous granular sodium sulfate, and evaporated under nitrogen. The residue is treated with excess diazomethane in ether-methanol, re-dried and dissolved in a small volume of chloroform. Samples are streaked on silica gel GF thin layer chromatography plates (Analtech, 5 cm. lanes) developed in acetone-benzene (2:3), and stained with I_2 vapor.

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Two bands are located according to standards (C, cholate, and D, dihydroxy bile acids) and scraped into scintillation vials containing 1 ml ethanol. Ten ml of triton-toluene scintillation fluid (1:2, 40 gm Omnifluor per liter) are added; radioactivity and external standard ratio are determined (Beckman LS-230, narrow ^{3}H and ^{14}C channels). Alternatively, C-band scrapings are mixed with 1.0 ml iso-propanol and centrifuged; cholate is determined in duplicate 0.10 ml samples of supernatant; the remainder, including residual silica gel is counted. Calculations are performed by PDP-10 computer program. Untreated controls are run daily and positive controls at frequent intervals (2% cholestyramine is run as standard). /Omnifluor is a blend of 98% 2,5-diphenyloxazole and 2% p-bis-(o-methylstyryl)-benzene, available from New England Nuclear Corp., Boston, Massachusetts, U.S.A./.

Several of the compounds described herein, but by no means all, have exhibited toxic effects when administered to animals at high doses. For example, oral administration of 6-chloro-N-/1-(1,2,3,6-tetrahydropyridyl)-carbonyl/nicotinamide to dogs at 250 mg/kg, ten times the projected efficacious dose, resulted in death of the dogs, with pathological signs suggestive of cardiac impairment. Administration of this agent at the same high dose to rats caused only moderate toxicological symptoms, including lethargy, diminished appetite and weight gain, and slight abnormalities in clinical chemistry.

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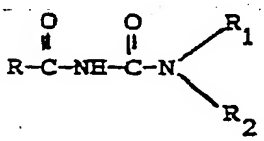
The compounds were tested for acute toxicity in the following manner. Healthy male CD-1 mice (20-25 g), 10 mice per group, received a single high dose of drug by intraperitoneal administration (1000 mg/kg in 0.6% Tween 20, at a concentration of 70 mg/ml). (Tween 20, polyoxyethylene sorbitan monolaurate, available from Atlas Chemical Industries Inc.). The animals were observed continuously for at least two hours, again at 24 hours and daily thereafter for one week. Controls received vehicle alone, 1.43 ml/kg and were asymptomatic throughout. The compounds tested and the widely varying mortality rates observed are tabulated below.



R	NR_1R_2	Mortality Rate
6-chloro-3-pyridyl	1-(1,2,3,6-tetrahydropyridyl)	0/10
3-pyridyl	1-(1,2,3,6-tetrahydropyridyl)	9/10
5-thiazolyl	$N-(n-C_4H_9)_2$	4/10
2-chloro-3-pyridyl	$NH(CH_2C_6H_5)$	0/10
3-pyridyl	$N-(n-C_4H_9)_2$	10/10

In seven-day chronic toxicity tests on healthy male CD-1 mice, 5 mice per group, daily doses of 500 mg/kg orally in 0.1% methyl cellulose for 5 days, 6-chloro-N-[1-(1,2,3,6-tetrahydropyridyl)carbonyl] nicotinamide produced hepatotoxicity.

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On the other hand, 2-chloro-N-(benzylaminocarbonyl)-nicotinamide and N-/1-(1,2,3,6-tetrahydropyridyl)carbonyl/quinoline-3-carboxamide showed no hepatotoxicity in the same test at the same high doses.

Despite the observation of toxicity of certain of the compounds of this invention at high dose levels in certain animal species; that is, at dose levels ten times the projected efficacious dose; said compounds are effective and useful for dissolving cholesterol gallstones in mammals at dose levels substantially below those at which toxicity is observed.

Particularly preferred individual compounds of the invention are the following:

5-chloro-N-/1-(1,2,3,6-tetrahydropyridyl)carbonyl/ nicotinamide,

N-/1-(1,2,3,6-tetrahydropyridyl)carbonyl/quinoline-3-carboxamide,

6-chloro-N-/(4-chloropiperidino)carbonyl/ nicotinamide,

N-/benzylaminocarbonyl/nicotinamide,

2-chloro-N-/benzylaminocarbonyl/nicotinamide,

6-chloro-N-/thiomorpholinocarbonyl/nicotinamide,

4-methyl-N-/di-n-butylaminocarbonyl/thiazole-5-carboxamide.

EXAMPLE 1

6-Chloro-N-[1-(1,2,3,6-tetrahydropyridyl)carbonyl]nicotinamide

To a solution of 6-chloronicotinamide (3.13 g, 0.020 mole) in dry ethylene dichloride (75 ml) under a nitrogen atmosphere is added oxalyl chloride (2.86 g, 0.022 mole) and the resulting suspension stirred and heated at 85°C for 90 minutes. The reaction mixture, now a clear solution, is cooled to 20°C. Then 1,2,3,6-tetrahydropyridine (7.32 g, 0.088 mole) is added dropwise, with stirring, at such a rate as to maintain a temperature of 20 - 30°C. Upon completion of addition, the mixture is stirred an additional half hour at room temperature. Hexane (150 ml) is added and the mixture extracted with 1N sodium hydroxide (100 ml) and then with water (100 ml). The extracts are combined, filtered and acidified with acetic acid to pH 5.5. The crystalline product which precipitates is filtered, oven dried at 70°C. Yield 4.80 g (90.3%); m.p. 152 - 154°C. Upon recrystallisation from hot ethyl acetate and drying, the product melts at 158-159.5°C. Yield 4.085 g.

Analysis:

Calculated for $C_{12}H_{12}O_2N_3Cl$: C, 54.24; H, 4.55; N, 15.81%

Found : C, 54.30; H, 4.33; N, 16.12%.

EXAMPLE 2

N-(Hexamethyleneiminocarbonyl)isonicotinamide

A mixture of isonicotinamide (2.45 g, 0.02 mole), tetrahydrofuran (250 ml) and oxalyl chloride (2.08 ml, 0.024 mole) is refluxed under a nitrogen atmosphere for 3.5 hours and is then cooled to room temperature. Hexamethyleneimine (9 ml, 0.08 mole) is added and the reaction stirred for one hour at room temperature. Benzene (200 ml) is added and the resulting mixture extracted with water (50 ml). The extract contains largely isonicotinamide. The reaction mixture is extracted with 1N sodium hydroxide (50 ml), the extract acidified with acetic acid and then extracted with ethyl acetate. Concentration of the ethyl acetate extract affords 0.7 g of oil which crystallises from ethyl acetate-hexane (1:1). Yield 128 mg (2.6%); m.p. 125 - 127°C.

Analysis:

Calculated for $C_{13}H_{17}O_2N_3$:	C, 63.14; H, 6.93; N, 16.99%
Found:	C, 63.03; H, 6.92; N, 17.07%

EXAMPLE 3

N-(Di-isopentylaminocarbonyl)nicotinamide

To a mixture of nicotinamide (24.4 g, 0.20 mole) and dry ethylene dichloride (2500 ml) is added oxalyl chloride (38.1 g, 0.30 mole). The mixture is then heated to reflux for 4.5 hours and then cooled to room temperature. It is filtered to give a clear pale orange solution of nicotinyl isocyanate which is used directly in the next step.

Over a ten minute period a solution of diphenylamine (50.7 g 0.30 mole) in dry ethylene dichloride (100 ml) is added to the isocyanate solution. A precipitate forms immediately and the suspension is stirred at room temperature for an additional half hour. The reaction mixture is filtered, the filter cake washed with ether and air dried. It is slurried in ether (2000 ml), filtered and dried. Yield = 39 g m.p. 141 - 146°C. The dry crystals are dissolved in 1N sodium hydroxide (350 ml), immediately filtered and the filtrate acidified with glacial acetic acid. The off-white precipitate of N-(diphenylaminocarbonyl)nicotinamide is filtered and dried at 50°C. Yield = 26.3 g (42%); m.p. 142 - 145°C.

A mixture of N-(diphenylaminocarbonyl)nicotinamide (1.6 g, 0.005 mole), toluene (50 ml), diisopentylamine (2.4 g, 0.015 mole) and glacial acetic acid (0.86 ml) is heated and stirred at 95 - 97°C for one hour.

The mixture is cooled to room temperature and extracted with 1N sodium hydroxide (50 ml). The extract is acidified with glacial acetic acid and the oil which separates extracted with ethyl acetate. Evaporation of the extract under reduced pressure gives 1.9 g of oil. The oil is taken up in ether (20 ml), the solution made acid with ethyl acetate-HCl and then diluted with an equal volume of hexane to precipitate a gum. Trituration of the gum with acetone (10 ml) affords the crystalline product. Yield = 1.04 g (61%); m.p. 112 - 115°C.

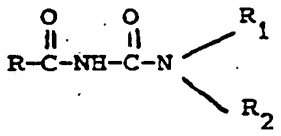
Analysis:

Calculated for $C_{17}H_{27}O_2N_3.HCl$: C, 59.72; H, 8.25; N, 12.29%

Found: C, 59.29; H, 8.15; N, 12.43%.

EXAMPLE 4

The following compounds are prepared from appropriate reactants according to the procedures of Examples 1, 2 or 3.



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R	NR_1R_2	M.P. (°C.)	Method of Example
3-pyridyl	NH_2	223-228	1
3-pyridyl	$NH(CH_3)$	222-223[a]	1
3-pyridyl	$NH(C_2H_5)$	195-197[a]	1
3-pyridyl	$NH(CH_2)_5CH_3$	76-77	3
3-pyridyl	$NH(CH_2)_9CH_3$	66-68	3
3-pyridyl	$N(CH_3)_2$	90-92	1
3-pyridyl	$N(n\text{-}C_3H_7)_2$	138-140[a]	1
3-pyridyl	$N(n\text{-}C_4H_9)_2$	112-115[a]	2
3-pyridyl	$N[(CH_2)_2CH(CH_3)_2]_2$	112-115[a]	3
3-pyridyl	$N[CH_2CH(CH_3)_2]_2$	143-147[a]	2
3-pyridyl	piperidino	162-164	1
3-pyridyl	4-methylpiperidino	105-108	1
3-pyridyl	4-(n-propyl)piperidino	121-123	1
3-pyridyl	4-(3-phenylpropyl)piperidino	93-96	1
3-pyridyl	4-chloropiperidino	118-120	1
3-pyridyl	4-benzylpiperidino	121-122	1
3-pyridyl	thiomorpholino	179-181	1
3-pyridyl	3-methylpiperidino	143-145	1
3-pyridyl	morpholino	165-166	1
3-pyridyl	1-azacycloheptyl	136-138	1

R	NR_1R_2	M.P. (°C.)	Method of Example
3-pyridyl	1-azacyclooctyl	93-96	1
3-pyridyl	3-(2,3,4,5-tetrahydro-3,1-benzazepinyl)	155-517	1
3-pyridyl	1-(1,2,3,6-tetrahydropyridyl)	171-173[a]	3
3-pyridyl	$NH(C_6H_5)$	223-226[a]	3
3-pyridyl	$NH(C_6H_{11})$	145-146	1
3-pyridyl	$NH(CH_2C_6H_5)$	156-518	2
3-pyridyl	NH(1-naphthyl)	232-235[a]	3
3-pyridyl	$NH(n\text{-}C_4H_9)$	98-100	2
4-pyridyl	$NH(CH_3)$	220-222	2
4-pyridyl	$NH(C_2H_5)$	172-175	2
4-pyridyl	$NH(n\text{-}C_4H_9)$	107-109	2
4-pyridyl	$NH(CH_2)_5CH_3$	78-81	2
4-pyridyl	$N(CH_3)_2$	165-167	2
4-pyridyl	$N(n\text{-}C_3H_7)_2$	138-141	2
4-pyridyl	$N[(CH_2)_2CH(CH_3)_2]_2$	150-155	2

R	NR_1R_2	M.P. (^oC)	Method of Example
4-pyridyl	$N(n\text{-}C_4H_9)_2$	220 (dec.)	2
4-pyridyl	piperidino	143-145	1
4-pyridyl	1-(1,2,3,6-tetrahydropyridyl)	117-119	1
4-pyridyl	1-azacycloheptyl	125-127	2
5-chloro-3-pyridyl	1-(1,2,3,6-tetrahydropyridyl)	133-135	1
6-chloro-3-pyridyl	NH_2	244-246	1
6-chloro-3-pyridyl	$NH(CH_3)$	235-237	1
6-chloro-3-pyridyl	$NH(n\text{-}C_4H_9)$	172-174	1
6-chloro-3-pyridyl	$NH(CH_2)_5CH_3$	143-145	1
6-chloro-3-pyridyl	$NH(CH_2)_6CH_3$	143-145	1
6-chloro-3-pyridyl	$NH(CH_2C_6H_5)$	191-192	1
6-chloro-3-pyridyl	$NH(C_6H_{11})$	220-222	1
6-chloro-2-pyridyl	$N(CH_3)_2$	121-123(b)	1

R	NR_1R_2	M.P. (°C.)	Method of Example
6-chloro-3-pyridyl	$N(n\text{-}C_3H_7)_2$	87-89 (b)	1
6-chloro-3-pyridyl	$N(n\text{-}C_4H_9)_2$	123-125 (b)	1
6-chloro-3-pyridyl	piperidino	150-152	1
6-chloro-3-pyridyl	morpholino	144-146	1
6-chloro-3-pyridyl	3-methylpiperidino	115-116	1
6-chloro-3-pyridyl	thiomorpholino	143-145	1
6-chloro-3-pyridyl	4-(3-phenylpropyl)piperidino	138-140	1
6-chloro-3-pyridyl	2-methylpiperidino	143-145	1
6-chloro-3-pyridyl	1-azacycloheptyl	108-110	1
6-chloro-3-pyridyl	1-azacyclooctyl	117-119	1
6-chloro-3-pyridyl	4-chloropiperidino	157-159	1
6-chloro-3-pyridyl	4-(n-propyl)piperidino	130-132	1
6-chloro-3-pyridyl	4-benzylpiperidino	152-154	1
6-chloro-3-pyridyl	3-(2,3,4,5-tetrahydro-3,1-benzazepinyl)	170-172	1
6-chloro-3-pyridyl	$N[CH_2CH(CH_3)_2]_2$	108-110	1
6-chloro-3-pyridyl	$N[(CH_2)_2CH(CH_3)_2]_2$	69-71	1

R	NR_1R_2	M.P. (°C)	Method of Example
6-chloro-3-pyridyl	4-methylpiperidino	137-139	1
6-chloro-3-pyridyl	$N[CH(CH_3)CH_2CH_3]_2$	142-144	1
6-chloro-2-pyridyl	NH_2	273-275	1
6-chloro-2-pyridyl	$NH(n\text{-}C_4H_9)$	108-110	1
6-chloro-2-pyridyl	$NH(CH_2)_9CH_3$	90-92	1
6-chloro-2-pyridyl	$NH(CH_2C_6H_5)$	190-191	1
6-chloro-2-pyridyl	$N(CH_3)_2$	207-209	1
6-chloro-2-pyridyl	piperidino	155-156	1
6-chloro-2-pyridyl	1-(1,2,3,6-tetrahydropyridyl)	115-116	1
6-chloro-2-pyridyl	$N(n\text{-}C_4H_9)_2$	81-83	1
3-quinolyl	$NH(C_2H_5)$	222-224	1
3-quinolyl	$NH(n\text{-}C_4H_9)$	164-166	1
3-quinolyl	$N(n\text{-}C_4H_9)_2$	108-110	1
3-quinolyl	$N[CH_2CH(CH_3)_2]_2$	141-143	1
3-quinolyl	1-azacycloheptyl	146-148	1
3-quinolyl	4-benzylpiperidino	188-190	1

R	NR_1R_2	M.P. (°C.)	Method of Example
3-quinolyl	2-methylpiperidino	142-144	1
3-quinolyl	piperidino	152-154	2
3-quinolyl	1-(1,2,3,6-tetrahydropyridyl)	157-159	2
5-quinolyl	piperidino	190-193	2
3-methyl-5-isoxazolyl	NH_2	264-265	1
3-methyl-5-isoxazolyl	$NH(C_2H_5)$	199-200	1
3-methyl-5-isoxazolyl	$N(CH_3)_2$	112-113	1
3-methyl-5-isoxazolyl	$N(n\text{-}C_3H_7)_2$	79-80	1
3-methyl-5-isoxazolyl	$NH(C_6H_5)$	206-207	1
3-methyl-5-isoxazolyl	piperidino	121-122	1
3-methyl-5-isoxazolyl	morpholino	125-126	1
3-methyl-5-isoxazolyl	thiomorpholino	162-164	1
3-methyl-5-isoxazolyl	4-chloropiperidino	180-182	1
3-methyl-5-isoxazolyl	4-methoxypiperidino	113-115	1
3-methyl-5-isoxazolyl	4-benzylpiperidino	128-130	1
3-methyl-5-isoxazolyl	3-methylpiperidino	121-123	1

R	NR_1R_2	M.P. (°C.)	Method of Example
3-methyl-5-isoxazolyl	4-methylpiperidino	115-116	1
3-methyl-5-isoxazolyl	2-methylpiperidino	118-119	1
3-methyl-5-isoxazolyl	4-n-propylpiperidino	127-129	1
3-methyl-5-isoxazolyl	1-azacycloheptyl	114-116	1
3-methyl-5-isoxazolyl	1-azacyclooctyl	108-110	1
3-methyl-5-isoxazolyl	4-(3-phenylpropyl)piperidino	116-118	1
3-methyl-5-isoxazolyl	1-(1,2,3,6-tetrahydropyridyl)	103-105	1
3-methyl-5-isoxazolyl	3-(2,3,4,5-tetrahydro-3,1-benzazepinyl	150-152	1
5-methyl-3-isoxazolyl	$N(CH_3)_2$	78-79	1
5-methyl-3-isoxazolyl	piperidino	100-101	1
3-phenyl-5-methyl-4-isoxazolyl	NH_2	204-206	1
3-phenyl-5-methyl-4-isoxazolyl	$N(CH_3)_2$	117-119	1
3-phenyl-5-methyl-4-isoxazolyl	$N(n\text{-}C_3H_7)_2$	135-136	1
3-phenyl-5-methyl-4-isoxazolyl	piperidino	133-135	1
3-phenyl-5-methyl-4-isoxazolyl	1-azacyclooctyl	127-219	1

R	NHR_1R_2	M.P. (°C)	Method of Example
3-phenyl-5-methyl-4-isoxazolyl	1-(1,2,3,6-tetrahydropyridyl)	127-129	1
4-methyl-5-oxazolyl	$NH(n\text{-}C_3H_7)$	104-106	1
4-methyl-5-oxazolyl	$N(CH_3)_2$	120-123	1
4-methyl-5-oxazolyl	piperidino	85-93	1
4-methyl-5-oxazolyl	1-(1,2,3,6-tetrahydropyridyl)	147-149	1
4-methyl-5-thiazolyl	$NH(CH_3)$	173-174	1
4-methyl-5-thiazolyl	$NH(C_2H_5)$	148-150	1
4-methyl-5-thiazolyl	$NH(n\text{-}C_4H_9)$	103-104.5	1

R	NR_1R_2	M.P. (°C.)	Method of Example
4-methyl-5-thiazolyl	$NH(CH_2)_5CH_3$	99-100.5	1
4-methyl-5-thiazolyl	$N(CH_3)_2$	106-108	1
4-methyl-5-thiazolyl	$N(C_2H_5)_2$	72-75	1
4-methyl-5-thiazolyl	$N(n\text{-}C_4H_9)_2$	63-65	1
4-methyl-5-thiazolyl	piperidino	103-105	1
4-methyl-5-thiazolyl	1-(1,2,3,6-tetrahydropyridyl)	129-132	1
5-isothiazolyl	NH_2	249-251	1
5-isothiazolyl	$NH(CH_2)_5CH_3$	103-105	1
5-isothiazolyl	$N(CH_3)_2$	112-114	1
5-isothiazolyl	piperidino	144-146	1
5-isothiazolyl	1-azacycloheptyl	119-121	1
5-isothiazolyl	1-(1,2,3,6-tetrahydropyridyl)	142-143	1
3-isothiazolyl	NH_2	198-200	3
3-isothiazolyl	$N(C_6H_5)_2$	134-136	3
3-isothiazolyl	piperidino	186-188	2
4-isothiazolyl	NH_2	252-253	1
4-isothiazolyl	$NH(C_2H_5)$	171-172	1

R	NR_1R_2	M.P. (°C.)	Method of Example
4-isothiazolyl	$N(CH_3)_2$	181-182	1
4-isothiazolyl	$N(n\text{-}C_3H_7)_2$	130-131	1
4-isothiazolyl	$NH(C_6H_{11})$	115-116	1
4-isothiazolyl	piperidino	155-156	1
4-isothiazolyl	morpholino	142-143	1
4-isothiazolyl	1-azacycloheptyl	134-135	1

R	NR_1R_2	M.P. (°C)	Method of Example
4-isothiazolyl	1-(1,2,3,6-tetrahydropyridyl)	132-133.5	1
3-methyl-5-isothiazolyl	NH_2	191-193	1
3-methyl-5-isothiazolyl	$N(CH_3)_2$	127-219	1
3-methyl-5-isothiazolyl	$NH(CH_2)_5CH_3$	123-125	1
3-methyl-5-isothiazolyl	piperidino	137-139	1
3-methyl-5-isothiazolyl	1-azacycloheptyl	123-125	1
3-methyl-5-isothiazolyl	1-(1,2,3,6-tetrahydropyridyl)	154-155	1
5-methyl-1,2,3-thiadiazolyl	piperidino	123-125	2
4-(1,2,3-thiadiazolyl)	$NH(CH_2)_5CH_3$	153-155	1
4-(1,2,3-thiadiazolyl)	$N(CH_3)_2$	179-181	1
4-(1,2,3-thiadiazolyl)	piperidino	157-159	1
4-(1,2,3-thiadiazolyl)	1-(1,2,3,6-tetrahydropyridyl)	136-138	1
4-(1,2,5-thiadiazolyl)	piperidino	135-137	1
3-(benzisothiazolyl)	NH_2	174-176	1
3-(benzisothiazolyl)	$N(CH_3)_2$	152-154	1
3-(benzisothiazolyl)	piperidino	116-118	1
3-(benzisothiazolyl)	1-(1,2,3,6-tetrahydropyridyl)	133-135	1
2-furyl	$N(CH_3)_2$	110-112	2
2-furyl	piperidino	145-146	2
5-thiazolyl	$N(n\text{-}C_4H_9)_2$	63-65	2
2-chloro-3-pyridyl	$NH(CH_2C_6H_5)$	190-191	1

(a) as hydrochloride
(b) as hydrate

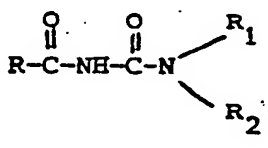
EXAMPLE 5

Isonicotinoyl Urea

Urea (7.5 g, 0.125 mole) is suspended in liquid ammonia (250 ml) in a round bottom flask fitted with an acetone/dry ice condenser. Sodium pellets (2.9 g, 0.125 mole) are added and, after they have dissolved, methyl isonicotinate (12 g, 0.089 mole) is added to the mixture. The ammonia is allowed to evaporate from the mixture overnight. The yellow-tan residue is dissolved in water (150 ml), the pH of the mixture adjusted to 5.5 with glacial acetic acid, and the precipitate which forms filtered, washed with water and air dried. It is then washed with hexane and triturated with boiling methanol. The white solid (isonicotinic acid) is removed by filtration and the filtrate evaporated to dryness to give the title product as a yellowish solid: m.p. 245 - 247°C. Quantitative analysis and infra-red data are consistent with the values expected for the product.

EXAMPLE 6

The compounds tabulated below are prepared from appropriate reactants by the procedures of Examples 1-3 or 5.



R	NR_1R_2	Method of Example
3-pyridyl	$N(C_6H_5)_2$	3
3-pyridyl	$NH(C_3H_5)$	1
3-pyridyl	4-methoxypiperidino	1
3-pyridyl	4-n-butoxypiperidino	1
3-pyridyl	3-chloropiperidino	1
4-pyridyl	$NH(C_6H_5)$	1
4-pyridyl	$N(C_6H_5)_2$	2
4-pyridyl	$N[(CH_2)_9CH_3]_2$	1
4-pyridyl	$NH(CH_2C_6H_5)$	2
4-pyridyl	$NH[(CH_2)_4C_6H_5]$	1
4-pyridyl	$N(CH_3)(C_6H_5)$	1
4-pyridyl	$N(n\text{-}C_3H_7)(CH_2C_6H_5)$	2
4-pyridyl	morpholino	1
4-pyridyl	thiomorpholino	1
4-pyridyl	NH(1-naphthyl)	1
4-pyridyl	4-methylpiperidino	1
4-pyridyl	2-ethoxypiperidino	1
4-pyridyl	4-n-propylpiperidino	2

R	NR_1R_2	Method of Example
4-pyridyl	4-chloropiperidino	2
4-pyridyl	4-(3-phenylpropyl)piperidino	1
4-pyridyl	3-(2,3,4,5-tetrahydro-3,1-benzazepinyl)	1
5-chloro-3-pyridyl	NH_2	1
5-chloro-3-pyridyl	$N(CH_3)(C_6H_5)$	2
5-chloro-3-pyridyl	$N(CH_3)(n\text{-}C_4H_9)$	2
5-chloro-3-pyridyl	$N(CH_3)(CH_2C_6H_5)$	1
5-chloro-3-pyridyl	$N(C_6H_5)_2$	3
5-chloro-3-pyridyl	piperidino	3
5-chloro-3-pyridyl	2-chloropiperidino	3
5-chloro-3-pyridyl	4-ethylpiperidino	3
5-chloro-3-pyridyl	4-benzylpiperidino	1
5-chloro-3-pyridyl	$NH(CH_2)_8CH_3$	2
5-chloro-3-pyridyl	4-ethoxypiperidino	1
5-chloro-3-pyridyl	morpholino	1
5-chloro-3-pyridyl	thiomorpholino	1

R	NR_1R_2	Method of Example
5-chloro-3-pyridyl	1-azacyclooctyl	2
5-chloro-3-pyridyl	$NH(C_4H_7)$	1
5-chloro-3-pyridyl	$N(CH_3)(C_6H_{11})$	1
5-chloro-3-pyridyl	NH(1-naphthyl)	2
2-chloro-3-pyridyl	$NH(C_6H_5)$	1
2-chloro-3-pyridyl	$N(CH_3)C_6H_5$	1
2-chloro-3-pyridyl	$N(n\text{-}C_3H_7)(CH_2C_6H_5)$	1
2-chloro-3-pyridyl	$N[(CH_2)_5CH_3]_2$	2
2-chloro-3-pyridyl	$N(CH_3)(C_6H_{11})$	2
2-chloro-3-pyridyl	4-(4-phenylbutyl)piperidino	1
2-chloro-3-pyridyl	1-azacycloheptyl	3
2-chloro-3-pyridyl	morpholino	3

R	NR_1R_2	Method of Example
2-chloro-3-pyridyl	4-methoxypiperidino	1
2-chloro-3-pyridyl	$N(n\text{-}C_6H_{13})CH_2C_6H_5$	1
2-chloro-3-pyridyl	NH(1-naphthyl)	2
2-chloro-3-pyridyl	4-n-butylpiperidino	3
2-chloro-3-pyridyl	2-methoxypiperidino	1
2-pyridyl	NH_2	5
2-pyridyl	$NH(CH_3)$	1
2-pyridyl	$NH[(CH_2)_9CH_3]$	1
2-pyridyl	NHC_6H_5	1
2-pyridyl	$NH(CH_2C_6H_5)$	2
2-pyridyl	$N(CH_3)(CH_2C_6H_5)$	2
2-pyridyl	$N(n\text{-}C_3H_7)(C_6H_5)$	1
2-pyridyl	$NH(C_6H_{11})$	2
2-pyridyl	NH-(1-naphthyl)	1
2-pyridyl	$N(CH_3)$(1-naphthyl)	1
2-pyridyl	$N(n\text{-}C_4H_9)$(1-naphthyl)	1
2-pyridyl	$N(CH_3)(n\text{-}C_6H_{13})$	1
2-pyridyl	$N(CH_3)(C_6H_{11})$	1

R	NR_1R_2	Method of Example
2-pyridyl	piperidino	2
2-pyridyl	3-ethylpiperidino	1
2-pyridyl	3-n-propoxypiperidino	1
2-pyridyl	thiomorpholino	2
2-pyridyl	2-chloropiperidino	1
2-pyridyl	4-benzylpiperidino	1
2-pyridyl	1-(1,2,3,6-tetrahydropyridyl)	1
3-quinolyl	NH_2	5
4-quinolyl	1-(1,2,3,6-tetrahydropyridyl)	1
5-quinolyl	1-(1,2,3,6-tetrahydropyridyl)	1
6-quinolyl	1-(1,2,3,6-tetrahydropyridyl)	1
7-quinolyl	1-(1,2,3,6-tetrahydropyridyl)	1
8-quinolyl	1-(1,2,3,6-tetrahydropyridyl)	1

R	NR_1R_2	Method of Example
5-quinolyl	NH_2	5
8-quinolyl	NH_2	5
4-quinolyl	$NH(CH_2C_6H_5)$	1
4-quinolyl	$NH(CH_2)_9CH_3$	1
4-quinolyl	$N(n\text{-}C_4H_9)_2$	5
2-quinolyl	$NH(CH_2C_6H_5)$	1
2-quinolyl	NH_2	5
2-quinolyl	1-(1,2,3,6-tetrahydropyridyl)	1
2-quinolyl	$NH[(CH_2)_9CH_3]$	1
5-quinolyl	piperidino	1
6-quinolyl	$N(CH_3)(C_6H_{11})$	1
6-quinolyl	1-azacyclooctyl	1
7-quinolyl	$N(n\text{-}C_4H_9)_2$	1
3-methyl-5-isoxazolyl	$NH(C_5H_9)$	1
3-methyl-5-isoxazolyl	$N(CH_3)(n\text{-}C_7H_{15})$	1
3-methyl-5-isoxazolyl	$N(C_2H_5)(C_6H_5)$	1

R	NR_1R_2	Method of Example
3-methyl-5-isoxazolyl	$N(n\text{-}C_3H_7)(C_6H_{11})$	2
3-methyl-5-isoxazolyl	4-(2-phenylethyl)piperidino	1
3-methyl-5-isoxazolyl	3-ethoxypiperidino	1
5-methyl-3-isoxazolyl	NH_2	5
5-methyl-3-isoxazolyl	morpholino	1
5-methyl-3-isoxazolyl	$NH(CH_2C_6H_5)$	1
5-methyl-3-isoxazolyl	$N[(CH_2)_2CH(CH_3)_2]_2$	1
5-methyl-3-isoxazolyl	1-(1,2,3,6-tetrahydropyridyl)	1
5-methyl-3-phenyl-4-isoxazolyl	thiomorpholino	2
5-methyl-3-phenyl-4-isoxazolyl	$NH[(CH_2)_6CH_3]$	3
5-methyl-3-phenyl-4-isoxazolyl	$N(C_6H_5)_2$	1
5-methyl-3-phenyl-4-isoxazolyl	$NH(C_3H_5)$	1
5-methyl-3-phenyl-4-isoxazolyl	$N(n\text{-}C_4H_9)(CH_2C_6H_5)$	1
5-methyl-3-phenyl-4-isoxazolyl	3-methylpiperidino	1
4-methyl-5-oxazolyl	NH_2	5
4-methyl-5-oxazolyl	$NH(C_6H_{11})$	5
4-methyl-5-oxazolyl	$N(C_2H_5)(C_6H_5)$	1
4-methyl-5-oxazolyl	$N(n\text{-}C_4H_9)(CH_2C_6H_5)$	2
4-methyl-5-oxazolyl	3-chloropiperidino	2
4-methyl-5-oxazolyl	$N(C_5H_9)(CH_3)$	1
4-methyl-5-oxazolyl	1-azacycloheptyl	1
4-methyl-5- xazolyl	4-(3-phenylpropyl)piperidino	1
4-methyl-5-oxazolyl	NH(1-naphthyl)	1

R	NR_1R_2	Method of Example
4-methyl-5-thiazolyl	NH_2	5
4-methyl-5-thiazolyl	$N[(CH_2)_5CH_3]_2$	1
4-methyl-5-thiazolyl	$N(CH_3)(i\text{-}C_3H_7)$	1
4-methyl-5-thiazolyl	$N(C_6H_5)_2$	3
4-methyl-5-thiazolyl	$N(n\text{-}C_4H_9)(CH_2C_6H_5)$	1
4-methyl-5-thiazolyl	4-ethylpiperidino	1
5-isothiazolyl	$N(n\text{-}C_4H_9)_2$	3
5-isothiazolyl	3-n-propoxypiperidino	1
5-isothiazolyl	$NH(C_6H_{11})$	1
5-isothiazolyl	$N(C_6H_5)(CH_2C_6H_5)$	1
3-isothiazolyl	$N(CH_3)(n\text{-}C_6H_{13})$	1
3-isothiazolyl	$N(CH_3)(n\text{-}C_{10}H_{21})$	1
3-isothiazolyl	morpholino	1
3-isothiazolyl	$N(n\text{-}C_4H_9)_2$	1
3-isothiazolyl	$N(C_2H_5)(CH_2C_6H_5)$	1
4-isothiazolyl	$N(C_6H_5)_2$	2
4-isothiazolyl	NH(1-naphthyl)	2
4-isothiazolyl	$NH(C_6H_{11})$	1
4-isothiazolyl	$N(C_6H_5)(C_6H_{11})$	1
4-isothiazolyl	$NH[C(CH_3)_3]$	1
3-methyl-5-isothiazolyl	$NHCH_2C_6H_5$	1
3-methyl-5-isothiaz lyl	$N(CH_3)(C_6H_5)$	1
3-methyl-5-isothiazolyl	$N[(CH_2)_9CH_3]_2$	2
3-methyl-5-isothiazolyl	4-(4-phenylbutyl)piperidino	1

R	NR_1R_2	Method of Example
3-methyl-5-isothiazolyl	$NH(C_4H_7)$	2
3-methyl-5-isothiazolyl	$N(C_2H_5)(n\text{-}C_6H_{13})$	1
3-methyl-5-isothiazolyl	morpholino	1
3-methyl-5-isothiazolyl	1-azacycloheptyl	1
3-methyl-5-isothiazolyl	3-chloropiperidino	1
4-(1,2,3-thiadiazolyl)	NH_2	5
4-(1,2,3-thiadiazolyl)	$NH(n\text{-}C_4H_9)$	5
4-(1,2,3-thiadiazolyl)	$NH(CH_2C_6H_5)$	1
4-(1,2,3-thiadiazolyl)	$N(C_6H_5)_2$	1
4-(1,2,3-thiadiazolyl)	$N(CH_3)(C_6H_{11})$	1
3-(1,2,5-thiadiazolyl)	NH_2	5
3-(1,2,5-thiadiazolyl)	$N(n\text{-}C_4H_9)_2$	1
3-(1,2,5-thiadiazolyl)	1-(1,2,3,6-tetrahydropyridyl)	1
3-(1,2,5-thiadiazolyl)	4-(n-butyl)piperidino	1
3-(1,2,5-thiadiazolyl)	4-(n-propoxy)piperidino	1
3-(1,2,5-thiadiazolyl)	$N(i\text{-}C_3H_7)_2$	1

R	NR_1R_2	Method of Example
3-(1,2,5-thiadiazolyl)	$NH(C_3H_5)$	1
3-benzisothiazolyl	$N[(CH_2)_2CH(CH_3)_2]_2$	1
3-benzisothiazolyl	$N(C_6H_5)(n\text{-}C_4H_9)$	1
3-benzisothiazolyl	$N(CH_3)(C_6H_{11})$	1
3-benzisothiazolyl	4-methylpiperidino	1
3-benzisothiazolyl	NH(1-naphthyl)	2
2-benzisothiazolyl	1-azacyclooctyl	1
3-benzisothiazolyl	morpholino	1
3-benzisothiazolyl	4-chloropiperidino	1
2-furyl	NH_2	5
2-furyl	$N(CH_3)(n\text{-}C_6H_{13})$	1
2-furyl	$NH(CH_2)_9CH_3$	1
2-furyl	1-(1,2,3,6-tetrahydropyridyl)	1
2-furyl	4-(3-phenylpropyl)piperidino	1

R	NR_1R_2	Method of Example
2-furyl	$N(C_2H_5)(C_6H_{11})$	2
2-furyl	$N(C_6H_5)_2$	2
2-furyl	$N(CH_3)(CH_2C_6H_5)$	1
2-furyl	NH(1-naphthyl)	1
3-furyl	NH_2	5
3-furyl	$N(n\text{-}C_4H_9)_2$	1
3-furyl	1-(1,2,3,6-tetrahydropyridyl)	1
3-furyl	piperidino	1
3-furyl	thiomorpholino	1
3-furyl	2-chloropiperidino	2
3-furyl	2-methylpiperidino	2
3-furyl	$N(n\text{-}C_4H_9)(C_6H_5)$	2
4-pyridyl	NH_2	5
2-chloro-3-pyridyl	4-(4-chlorophenyl)piperidino	1
4-pyridyl	4-(4-chlorophenyl)piperidino	1
3-quinolyl	4-(2-chlorophenyl) piperidino	1

R	NR_1R_2	Method of Example
3-methyl-5-isoxazolyl	4-(4-chlorophenyl)piperidino	1
5-methyl-3-isoxazolyl	4-(4-chlorophenyl)piperidino	1
3-(1,2,5-thiadiazolyl)	4-(4-chlorophenyl)piperidino	1
5-thiazolyl	1-(1,2,3,6-tetrahydropyridyl)	1
5-thiazolyl	$NH(CH_2C_6H_5)$	1
5-thiazolyl	1-azacyclooctyl	1
5-thiazolyl	$NH[(CH_2)_4C_6H_5)$	1
4-thiazolyl	$NH(CH_2C_6H_5)$	1
4-thiazolyl	1-(1,2,3,6-tetrahydropyridyl)	1
4-thiazolyl	$NH(CH_2)_9CH_3$	1
4-thiazolyl	$N(CH_3)(C_6H_5)$	1
4-thiazolyl	piperidino	1
5-thiazolyl	4-(3-phenylpropyl)piperidino	1

General Methods for Preparation of Amide Reactants

Method A

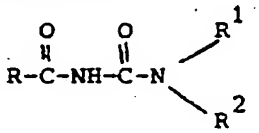
The appropriate acid reactant of formula R-COOH is heated to reflux in an excess of thionyl chloride for 3 hours. The reaction mixture is then evaporated to dryness under reduced pressure and the residue added in small portions with stirring to an excess of concentrated ammonium hydroxide at room temperature. The mixture is stirred for one hour following completion of addition and the product recovered by filtration if it is insoluble or by evaporation if it is soluble.

Method B

The appropriate nitrile reactant of formula R-CN is added to ethanol containing a 10% excess of potassium hydroxide. To the resulting mixture is added excess 30% hydrogen peroxide and the reaction mixture heated gently to 60°C. The reaction becomes exothermic and is cooled if necessary to maintain the temperature at about 60°C. The reaction is allowed to continue until oxygen evolution ceases. It is then concentrated under reduced pressure to small volume, the residue filtered, washed with water and dried.

CLAIMS

1. Heterocyclylcarbonyl ureas for use in dissolving gallstones having the formula:



wherein R is pyridyl, monochloro-pyridyl, quinolyl, furyl, thiazolyl, 4-methyl-5-thiazolyl, 4-methyl-5-oxazolyl, isothiazolyl, 3-methyl-5-isothiazolyl, 3-(1,2-benziso-thiazolyl), 5-methyl-3-isoxazolyl, 3-methyl-5-isoxazolyl, 5-methyl-3-phenyl-4-isoxazolyl, 3-(1,2,5-thiadiazolyl) or 4-(1,2,3-thiadiazolyl);

R^1 is hydrogen, alkyl having from one to ten carbon atoms naphthyl or phenyl;

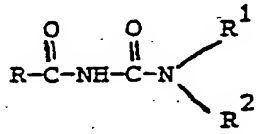
R^2 is hydrogen, alkyl having from one to ten carbon atoms, phenyl, or phenylalkyl wherein the alkyl has from one to four carbon atoms;

or R^1 and R^2 taken together with the nitrogen to which they are attached form a morpholino, thiomorpholino, 1-(1,2,3,6-tetrahydropyridyl), 1-azacycloheptyl, 1-azacyclooctyl or 3-(2,3,4,5-tetrahydro-3,1-benzazepinyl) group, or a piperidino group optionally substituted with alkyl having from one to four carbon atoms, alkoxy having from one to four carbon atoms, chloro, or phenylalkyl having from one to four carbon atoms in the alkyl group;

with the proviso that, where R is a 5-methyl-3-isoxazolyl group, then R^1 and R^2 are taken together with the nitrogen to which they are attached and form a group other than morpholino;

and the pharmaceutically acceptable acid addition salts of those compounds wherein R is a basic group.

2. Heterocyclylcarbonyl ureas having the formula:



wherein R, R^1 and R^2 are as defined in claim 1, with the further proviso that, when R is 3-pyridyl and R^1 is hydrogen, R^2 is other than hydrogen, methyl or ethyl.

3. Compounds as claimed in claim 1 or claim 2, in which R^1 is hydrogen and R^2 is a phenylalkyl group.

4. Compounds as claimed in claim 3, in which R^2 is a benzyl group.

5. Compounds as claimed in claim 1, or claim 2, in which R^1 and R^2 taken together with the nitrogen atom to which they are attached form a six-membered ring.

6. Compounds as claimed in claim 5, in which R^1 and R^2 taken together with the nitrogen atom to which they are attached form a 1-(1,2,3,6-tetrahydropyridyl) or an optionally-substituted piperidino group.

7. Compounds as claimed in any preceding claim in which R is a pyridyl, chloro-substituted pyridyl or quinolyl group.

8. A compound as claimed in claim 7 which is:

5-Chloro-N-/1-(1,2,3,6-tetrahydropyridyl)carbonyl/ nicotinamide;

N-/1-(1,2,3,6-tetrahydropyridyl)carbonyl/quinoline-3-carboxamide;

6-Chloro-N-/(4-chloropiperidino)carbonyl/ nicotinamide;

N-/Benzylaminocarbonyl/nicotinamide;

2-Chloro-N-/benzylaminocarbonyl/nicotinamide;

or 6-Chloro-N-/thiomorpholinocarbonyl/nicotinamide.

9. A compound as claimed in claim 1 or claim 2 which is 4-Methyl- N-/di-n-butylaminocarbonyl/thiazole-5-carboxamide.

10. A pharmaceutical composition comprising a compound as claimed in any preceding claim and a pharmaceutically acceptable carrier material.

European Patent Office

EUROPEAN SEARCH REPORT

0004187
Application number
EP 79 30 0351

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim
X	CHEMICAL ABSTRACTS. vol. 83, no. 3, published July, 21, 1975, page 473, column 2, nr. 27835b Columbus, Ohio, USA DOBYCHINA N.S. et al.: "Acylation of N-alkylureas" & Izv. Tomsk. Politekh. Inst. 1974, 198, 110-12.	2-4,7, 8
	--	
	FR - A - 2 120 032 (SHIONOGI) * Claims; page 1, lines 5-30; page 4, line 22 - page 5, line 8 *	1,2,5, 6,10
	--	
	US - A - 3 931 244 (J. LEHEUP ARCHIBALD) * Column 1, lines 8-34; column 2, lines 9-19; column 4, example 6 *	1-3,10
	--	
X	NL - A - 70 16613 (SHIONOGI) * Page 1, line 4 - page 2, line 3, page 3, lines 21-28 *	1,2,5, 6,10
D	& US - A - 4 014 876	

CLASSIFICATION OF THE APPLICATION (Int. Cl.³)

C 07 D 401/12
213/82
417/12
277/56
A 61 K 31/455
31/41
31/47//
C 07 D 413/12
213/81
215/54
261/18
275/02
275/04
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TECHNICAL FIELDS SEARCHED (Int.Cl.³)

C 07 D 213/82
401/12
215/54
275/02
263/34
277/56
261/18
285/06
285/10
213/81
275/04
307/68
A 61 K 31/455

CATEGORY OF CITED DOCUMENTS

X: particularly relevant
A: technological background
O: non-written disclosure
P: intermediate document
T: theory or principle underlying the invention
E: conflicting application
D: document cited in the application
L: citation for other reasons

&: member of the same patent family, corresponding document

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
The Hague	05-06-1979	NUYTS

EPO Form 1503.1 06.78

European Patent Office

EUROPEAN SEARCH REPORT

Application number
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DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int. Cl.³)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	C 07 D 307/68 407/12 263/34 285/06 285/10
			TECHNICAL FIELDS SEARCHED (Int. Cl.³)
			A 61 K 31/41 31/47